CLAIMS

What is claimed is:

1. A method of determining the haplotype structures of a nucleic acid comprising two or more single nucleotide polymorphisms (SNPs) of interest, wherein said SNPs of interest comprise different alleles, comprising:

obtaining an enriched nucleic acid fraction which comprises from 2 to 30 times more of one allelic variant of the nucleic acid than the other allelic variant of the nucleic acid; wherein said one allelic variant is an enriched allelic variant and the other allelic variant is a non-enriched allelic variant,;and

genotyping the enriched nucleic acid fraction to identify the alleles in said two or more SNPs of interest that are present at a higher level or lower level than the other alleles in said two or more SNPs of interest, wherein the alleles that are present at a higher level are on the enriched allelic variant and form one haplotype and the alleles that are present at a lower level are on the non-enriched allelic variant and form the other haplotype.

2. The method of claim 1 wherein the enriched nucleic acid fraction is obtained by preferentially extracting one allelic variant of the nucleic acid from a nucleic acid sample obtained from a subject.

3. The method of claim 2 wherein said one allelic variant is preferentially extracted from the nucleic acid sample by contacting the nucleic acid sample with an allele-specific hybridization probe that is fully complementary to a sequence of one allele of a heterozygous SNP site that is located within or near the target site, wherein said allele specific hybridization probe is attached to a solid support or to a first binding molecule that is capable of binding to a second binding molecule that is attached to a solid support, and wherein the nucleic acid sample and the allele-specific hybridization probe are contacted under hybridization conditions that allow the allele-specific hybridization probe to preferentially hybridize with said one allele of said heterozygous SNP site.

4. The method of claim 3 wherein said allele-specific hybridization probe is attached to a first binding molecule.

5. The method of claim 4 wherein the first binding molecule is biotin or streptavidin and said second binding molecule is streptavidin or biotin, respectively.

6. The method of claim 2 wherein the enriched nucleic acid fraction comprises the nucleic acid molecules that are extracted from the nucleic acid sample and the level of the enriched allelic variant in the enriched nucleic acid fraction is from 1.5 to 100 times greater that the level of the non-enriched allelic variant in the enriched nucleic acid fraction.

7. The method of claim 2 wherein the enriched nucleic acid fraction comprises the nucleic acid molecules that are not extracted from the nucleic acid sample.

8. The method of claim 1 further comprising the step of amplifying the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles in said two or more SNPs of interest that are present at a higher level or lower level in the enriched nucleic acid fraction than the other alleles in said two or more SNPs of interest, wherein said amplification proportionately increases the amount of the enriched allelic variant and the non-enriched allelic variant in the enriched nucleic acid fraction.

9. The method of claim 2 further comprising the step of amplifying the nucleic acids in the enriched nucleic acid fraction prior to identifying the alleles in said two or more SNPs of interest that are present at a higher level or lower level in the enriched nucleic acid fraction than the other alleles in said two or more SNPs of interest, wherein said amplification proportionately increases the amount of the enriched allelic variant and the non-enriched allelic variant in the enriched nucleic acid fraction.

10. The method of claim 8 wherein the nucleic acids in the enriched nucleic acid fraction are amplified by a polymerase chain reaction (PCR) amplification procedure which employs one or more primer sets that hybridize to sequences flanking said two or more SNPs of interest.

11. The method of claim 9 wherein the nucleic acids in the enriched nucleic acid fraction are amplified by a polymerase chain reaction (PCR) amplification procedure which employs one or more primer sets that hybridize to sequences flanking said two or more SNPs of interest.

12. The method of claim 2 wherein the allele-specific hybridization probe is an oligonucleotide, a peptide nucleic acid or a locked nucleic acid.

13. The method of claim 1 wherein the nucleic acid sample is a genomic DNA sample.

14. The method of claim 2 wherein the nucleic acid sample is a genomic DNA sample.

15. The method of claim 2 wherein the allele-specific hybridization probe is an oligonucleotide that is attached to a first binding molecule and said nucleic acid sample is contacted with both the allele-specific hybridization probe and a competitor olignucleotide that hybridizes to the other allele of the heterozygous SNP site and that is not attached to the first binding molecule.

16. The method of claim 1 wherein the enriched nucleic acid fraction comprises 3 to 6 times more of the enriched allelic variant than the non-enriched allelic variant.

17. The method of claim 2 wherein the genotype of the nucleic acid comprising the target site is determined before one allelic variants of the nucleic acid is extracted from the original nucleic acid sample.

18. A method of determining the haplotype structures of two allelic variants of a chromosome or chromosomal fragment comprising two or more single nucleotide polymorphisms (SNPs) of interest, wherein said SNPs of interest comprise different alleles, said method comprising:

preferentially extracting one of said two allelic variant from an original nucleic acid sample comprising said two allelic variants of said chromosome of chromosomal fragment to provide an enriched sample in which the level of the preferentially extracted allelic variant is from 2 to 30 times greater than the level of the allelic variant that is not preferentially extracted from the sample;

PCR amplifying the enriched sample to proportionately increase the level of the allelic variant that is preferentially extracted from the sample and the level of the allelic variant that is not preferentially extracted from the sample; and

identifying the alleles of the SNPs of interest that are present at higher levels in the amplified enriched sample and are located on the allelic variant that is preferentially extracted from the original nucleic acid sample; and

identifying the alleles of the SNPs of interest that are present at lower levels in the amplified enriched sample and are located on the allelic variant that is not preferentially extracted from the original nucleic acid sample.

19. The method of claim 18 wherein one of said allelic variants is preferentially extracted from said original nucleic acid sample by a solid phase extraction technique that employs an allele-specific hybridization probe that that is fully complementary to a sequence of one allele of a heterozygous SNP site that is located on said chromosome or chromosomal fragment, wherein said allele specific hybridization probe is attached to a solid support or to a first binding molecule that is capable of binding to a second binding molecule that is attached to a solid support.

20. The method of claim 19 wherein said allele-specific hybridization probe is an oligonucleotide that is attached to a first binding molecule, and said solid phase extraction technique also employs a competitor oligonucleotide that hybridizes to the other allele of the heterozygous SNP site and that is not attached to the first binding molecule

21. The method of claim 18 wherein the genotypes of the chromosomes or chromosomal fragments are determined before one allelic variant of the chromosomes or chromosomal fragments is extracted from the original nucleic acid sample.

22. The method of claim 18 wherein the amount of the enriched allelic variant in the enriched nucleic acid fraction is from 3 to 10 times greater than the amount of the non-enriched allelic variant in the nucleic acid sample.

23. A kit for determining the haplotypes of a genomic DNA sample comprising two or more SNPs of interest that comprise different alleles, comprising:

an allele-specific hybridization probe that comprises a sequence that is completely complementary to one of the alleles of one of said two or more SNPs of interest, said allele-specific hybridization probe further comprising a first binding molecule;

one or more primer sets that hybridize to sequences flanking said two or more SNPs of interest;

and a solid support attached to a second binding molecule that binds to said first binding molecule.